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(71) Applicant *(for all designated States except US)*: **GESELLSCHAFT FÜR BIOTECHNOLOGISCHE FORSCHUNG MBH (GBF)** [DE/DE]; Mascheroder Weg 1, 38124 Braunschweig (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **HOEFLE, Gerhard** [DE/DE]; Mascheroder Weg 1, 38124 Braunschweig (DE). **KARAMA, Usama** [EG/DE]; Alte Stöckener Strasse 100, 30419 Hannover (DE).

(74) Agents: **BOETERS, Hans, D.** et al.; Boeters & Bauer, Bereiteranger 15, 81541 München (DE).

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(54) Title: DEGRADATION OF EPOTHILONES

(57) Abstract: According to one embodiment the invention concerns a process for a degradation of an epothilone C or a epothilone D, wherein an epothilone C or epothilone D is subjected to an olefin metathesis in the presence of ethylene and subsequently an optional ester hydrolysis.

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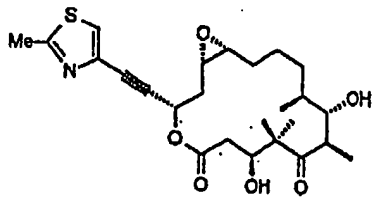
Degradation of Epothilones

Epothilones of type C and type D belong to the art and are especially characterized by a C=C double bond at positions 12 and 13 and a hydrogen atom at position 12 (type C) or an alkyl group-(type D).

According to one embodiment the invention concerns a process for a degradation of an epothilone C or an epothilone D, wherein an epothilone C or an epothilone D is subjected to an olefin metathesis in the presence of ethylene and subsequently an optional ester hydrolysis (scheme I).

According to the invention the epothilone C or D can be a fermentation product.

According to another embodiment the invention concerns a process for the production of an epothilone of formula 9



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wherein an epothilone of formula 2a (schemes I and II) is converted into compound of formula 3a (scheme II), the compound of formula 3a is reacted with a compound of formula 6 (which has been formed by reacting a compound of formula 4 with a compound of formula 5; scheme II) to give a compound of

formula 7 by esterification (scheme II), the compound of formula 7 is reacted in the presence of a Grubbs catalyst to give a compound of formula 8a by deprotection (scheme II), the compound of formula 8a is converted into a compound of formula 8b by deprotection (scheme II), and compound of formula 8b is converted to a compound of formula 9 by epoxidation (scheme II).

Alternatively to the reaction sequence depicted in scheme I synthetic intermediates of type 3 may be obtained according to scheme III by

1) cleavage of the lactone of epothilone C or D with e.g. pig liver esterase (PLE) or, after protection of the 3,7-hydroxyl groups, with aqueous base to give 10 (this conversion is described in U.S. Patent Application 09/811,808, March 19, 2001 by BMS/GBF),
2) optionally esterification with diazomethane and optionally protection of the 3,7-dihydroxyl groups to give 11,
3) olefin metathesis with an excess of an olefin, e.g. ethylene and a ruthenium or molybdenum metathesis catalyst and optionally protection of the 3,7-dihydroxyl groups to give 3b.

Experimental Part

12,13-seco-Epothilone C (2a):
450 mg of epothilone C (1) (0.95 mmol) were dissolved in 250 mL of dichloromethane, saturated with ethylene and after addition of 60 mg of Grubb's catalyst ($PhCHRuCl_2[P(Cy)_3]_2$ stirred for 24 hours. After addition of further 60 mg of catalyst and stirring for 24 hours the dark solution was evaporated to dryness and the residue purified by

chromatography on silica with the solvent system hexanes/tert.-butylmethylester/methanol 80:20:1. The first fraction contained 360 mg (75 %) of **2a**, the second 100 mg (22 %) of recovered starting material **1**.

2a: ^{1}H-NMR ($CDCl_3$), 300 MHz): δ = 6.95 (s, 19-H), 6.02 (s, 17-H), 5.89 - 5.64 (m, 12-H, 13-H), 5.16 - 4.89 (m, 12a-H_2, 13a-H_2), 5.37 (t, J = 7 Hz, 15-H), 4.24 (ddd, J = 10, 3, 3.5 Hz, 3-H), 3.36 (s, OH), 3.34 (d, J = 8 Hz, 7-H), 3.25 (dq, J = 1.5, 7 Hz, 8-H), 3.21 (d, J = 3.8 Hz, OH), 2.70 (s, 21-H_3), 2.52 - 2.32 (m, 2-H_2, 14-H_2), 2.07 (d, J = 1.5 Hz, 16-Me), 2.05 - 1.95 (m, 11-H_2), 1.8 - 1.1 (m, 6-H, 8-H, 9-H_2, 10-H_2), 1.18 (s, 4-Me), 1.10 (s, 4-Me), 1.04 (d, J = 7 Hz, 6-Me), 0.83 (d, J = 7 Hz, 8-Me).
ESI-MS (pos ions) m/z = 506 [M + H^+], CI - MS (NH_3 pos. ions) m/z = 506 [M + H^+] (22 %), 380 (100 %).

3,7-Di-[*tert*-buthyldimethyl-silyloxy]-4,4,6,8-tetramethyl-5-oxo-12-tridecenoic acid (3a)
To 330 mg (0.65 mmol) of 12,13-seco-epothilone C (**2a**) dissolved in 10 mL of THF were added with stirring 0.6 mL of NEt_3 and 0.6 mL of *tert*-butyldimethylsilyltriflate. After one hour the solvent was evaporated in vacuo. The residue was dissolved in 10 mL of THF, 70 mg of LiOH dissolved in 0.5 mL of water were added and the mixture stirred for 16 hours. The solvents were evaporated and the residue distributed between phosphate buffer of pH 5 and ethyl acetate. The organic layer was dried with $MgSO_4$ and evaporated to dryness. Preparative HPLC on RP-18 with the solvent system methanol/20 mmol ammonium acetate buffer pH 7 gave 235 mg (67 %) of **3a** as colorless viscous oil.

Analytical HPLC on Nucleosil RP-18 (260 x 5 mm) solvent system methanol/20 mmol ammonium acetate buffer pH 7, 1 mL/min, light scattering detector: R_t = 5.5 min.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 5.78 (m, 12-H), 4.99, 4.92 (m, 13-H_2), 4.39 (dd, J = 6.3, 3.4 Hz, 3-H), 3.79 (dd, J = 7.2, 2.0 Hz, 7-H), 3.12 (dq, J = 7.0 Hz, 8-H), 2.49 (dd, J = 16.5, 3.5 Hz, 2-H_a), 2.32 (dd, J = 16.5, 6.2 Hz, 2-H_b), 1.5 - 1.0 (m, 6-H, 8-H, 9-H_2, 10-H_2, 11-H_2), 1.2 (s, 4-Me), 1.07 (s, 4-Me), 1.04 (d, J = 6.9 Hz, 6-Me), 0.91 (d, J = 7.0 Hz, 8-Me), 0.89 (s, tBuSi), 0.88 (s, tBuSi), 0.09 (s, MeSi), 0.06 (s, MeSi), 0.05 (s, 2 MeSi).

ESI - MS (neg. ions) m/z = 541 (M-H) .

4-Bromo-2-methyl-thiazole (4)

1 g (2.05 mmol) 2,4-Dibromothiazole was dissolved in 25 mL anhydrous ether and the resulting solution was stirred under N_2 atmosphere at - 78°C. To the solution was added n-BuLi (1.1 equivalent, 4.52 mmol, 2.82 mL of 1.6 M solution in hexane) and the stirring was continued for 1 h. To the reaction mixture was then added dropwise a solution of dimethylsulfate 1.16 mL (12.34 mmol) in 1 mL ether. After stirring for 4 h at -78°C the reaction mixture was allowed to warm to room temperature and stirred for 14 h. The reaction mixture was diluted with a saturated solution of $NaHCO_3$ (10 mL). The aqueous layer was extracted with ether and the combined organic extracts were washed with a brine and dried over $MgSO_4$. Concentration under vacuum, and flash column chromatography (silica gel, 10:1 petroleum ether/ethyl acetate), yielded 0.52 g (70.6%) a yellow oil.

IR (KBr): 3122, 2923, 1485, 1441, 1252, 1178, 1085887, 834 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz) : δ = 7.02 (s, 1H), 2.71 (s, 3H).

^{13}C-NMR ($CDCl_3$, 100.6 MHz) : δ = 167.31, 124.18, 116.11, 19.40.
EI-MS (70 eV): m/z (%): 179 (93) $[M+2H]^+$, 177 (100) $[M+H]^+$, 169 (30), 164 (20), 159 (15).
HRMS (EI): calcd for C_4H_4BrNS 176.9251, found 176.9248

1-(2-methyl-thiazol-4-yl)-hex-5-en-1-yn-3-ol (6)
480 mg (2.68 mmol) 4-Bromo-2-methyl-thiazole (4) in 4 mL Et_3N was added to 131 mg (0.187 mmol) $PdCl_2(PPh_3)_2$ and the suspension was stirred 15 minutes under N_2 atmosphere at room temperature. then 117 mg (0.614 mmol) CuI was added under N_2 atmosphere followed by dropwise addition of 283 mg alcohol 5 (A.B. Smith, III et al. *JACS 120*, 3935-3948 (1998)) in 1 mL Et_3N. The mixture was stirred for 15 minutes at room temperature and heated to 80°C for 6 h. Concentration under vacuum, and flash column chromatography (silica gel, 3:2 petroleum ether/ethyl acetate), yielded 0.29 g (56 %) a yellow oil. [α] = - 29.1 (c= 1 in chloroform)

IR (KBr): 3386, 3142, 2924, 1641, 1501, 1435, 1286, 1194, 1041, 993, 918 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 400 MHz) : δ = 7.26 (s, 1H), 5.98-5.88 (m, 1 H), 5.23-5.16 (m, 2H), 4.62 (dd, *J*= 11.9, 5.8 Hz, 1H), 2.68 (3H, S), 2.58-2.54 (2H, m), 2.39 (d *J*= 6.1Hz, 1H, OH)
^{13}C-NMR (CDCl3, 75.5 MHz) : δ = 165.77, 136.20, 133.09, 122.48, 118.85, 89.53, 79.04, 61.84, 41.87, 19.10.
DCI-MS (NH_3): 211 $[M+NH_4^+]$, 194 $[M+H^+]$.

(1*S*)-1-[(2-Methyl-thiazole-4-yl)-1-ethynyl]-3-butenyl (3*S*,6*R*,7*S*,8*S*)-3,7-di-[tert-butyldimethylsiloxy]-4,4,6,8-tetramethyl-5-oxo-12-tridecenoate (7)
99 mg (0.478 mmol)DCC was added at 0°C to a solution of acid 200 mg(0.368 mmol), alcohol 79 mg (0.405 mmol) and 12 mg (0.09 mmol) DMAP in 10 mL CH_2Cl_2 . The mixture was stirred for 15 min

at 0°C and for 16 h at room temperature. Concentration under vacuum, and flash column chromatography (silica gel, 10:1 petroleum ether/ethyl acetate), yielded 240 mg (91%) a yellow oil.

$[\alpha]$ = - 45.8 (c= 1 in CH_2Cl_2)
IR (KBr): 2929, 2856, 1742, 1697, 1641, 1472, 1253, 989 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 400 MHz) : δ = 7.28 (s, 1H, thiazole H-5), 5.91-5.73 (m, 2H, H-12, H-3´),
5.58 (t, *J*= 6.1Hz, 1H,, H-1´), 5.20-4.90 (m, 4H, H-13, H-4´), 4.38 (dd, *J*= 6.3, 3.3 Hz, 1H, H-3), 3.74 (dd, *J*= 6.8, 2.2 Hz, 1H, H-7), 3.11 (dq, *J*= 6.8, 6.8 Hz, 1H, H-6), 2.67 (s, 3H, thiazole CH_3), 2.60 (t, *J*= 6.6Hz, 1H,, H-2), 2.55 (dd, *J*= 16.7, 3.5 Hz, 1H, H-2´), 2.29 (dd, *J*= 17.0, 63 Hz, 1H, H-2´), 2.05-1.95 (m, 2H, H-11), 1.47-1.29 (m, 3H,)1.17-1.08(m, 2H)(H-8, H-9, H-10), 1.21 (s, 3H, H-22), 1.05 (s, 3H, H-23), 1.03 (d, *J*= 6.6Hz, 3H, C6-CH_3), 0.89 (d, *J*= 6.6Hz, 3H, C8-CH_3), 0.88, 0.87(2s, 2x9H, $OSiC(CH_3)_3$), 0.089 (s, 3H, $OSi(CH_3)_2$) , 0.032, 0.028, 0.024 (3s, 3x3H, $OSi(CH_3)_2$) .
^{13}C-NMR ($CDCl_3$, 100.6 MHz) : 217.63, 170.84, 165.55, 138.97, 136.08, 132.23, 123.22, 118.91, 114.41, 85.67, 79.97, 73.76, 63.77, 53.38, 45.23, 40.20, 39.09, 38.87, 34.35, 34.00, 30.48, 27.11, 26.26, 26.07, 25.66, 24.97, 23.44, 19.89, 18.55, 17.66, 15.52, -3.61, -3.74, -4.20, -4.59
DCI-MS (NH_3): 735[M+NH_4^+], 718[M+H^+].
HRMS (DCI): calcd for $C_{39}H_{70}N_2O_5SSi_2$ 735.4622, found 735.4675.

(*4S,7R,8S,9S,16S*)-4,8-Di-tert-butyldimethylsilyloxy-5,5,7,9-tetramethyl-1-6-[2-(2-methyl-1,3-thiazol-4-yl)-1-ethynyl)-1-oxa-13-cyclohexadecen-2,6-dione, mixture of Z and E isomeres (8a)

To a solution of 190 mg (0.264 mmol) diene 7 in 66 mL CH_2Cl_2 was added 44 mg (0.053 mmol)

bis(tricyclohexylphosphine)benzylideneruthenium dichloride and the reaction mixture was stirred for 48 h at room temperature. Concentration under vacuum, and flash column chromatography (silica gel, 10:1 petroleum ether/ethyl acetate), yielded 95mg (52%) of a yellow oil.

(*4S,7R,8S,9S,16S*)-4,8-Dihydroxy-tert-5,5,7,9-tetra-methyl-1-6-[2-(2-methyl-1,3-thiazol-4-yl)-1-ethynyl)-1-oxa-13-cyclohexadecen-2,6-dione (8b), mixture of cis and trans isomere

A solution of 95 mg (0.137 mmol) lactone X in 12 mL CH_2Cl_2 at - 20°C was treated with 2 mL trifluoroacetic acid, and the mixture was stirred for 2 h at 0°C. After concentration under vacuum, the residue was diluted with EtOAC , washed with saturated $NaHCO_3$ solution and dried over $MgSO_4$. Concentration under vacuum, and separation by HPLC (80:20:3 hexane/t-BuOMe/ MeOH), yielded 27 mg (42 %) of the cis-hydroxy lactone **8b** and 27 mg (42 %) of the corresponding *trans* isomer.

[α] = - 123 (c= 1 in CH_2Cl_2)

^{1}H-NMR ($CDCl_3$, 400 MHz) : δ = 7.30 (s, 1H, H-19), 5.65 (dd,*J*= 9.1, 2.9 Hz, 1H, H-15), 5.55-5.41 (m, 2H, H-12, H-13), 4.20 (dd,*J*= 10.8, 2.7 Hz, 1H, H-3), 3.67-3.65 (m, 1H, H-7), 3.12 (dq, *J*= 6.6, 2.0 Hz, 1H, H-6), 2.88-2.77 (m, 1H, H-14), 2.70 (s, 3H, H-21), 2.51 (dd, *J*= 15.0Hz, 10.9 Hz, 1H, H-2), 2.27 (dd,*J*= 15.2, 2.8 Hz, 1H, H-2), 2.18-2.00 (m, 2H, H-11, H-14), 1.71-1.58 (m, 3H, H-8, H-9, H-10), 1.32 (s, 3H, H-22), 1.30-1.19 (3H, H-8, H-9, H-10), 1.18 (d, *J*= 6.7Hz, 3H, H-24), 1.07 (s, 3H, H-23), 0.98 (d, *J*= 6.9Hz, 3H, H-25)

^{13}C-NMR (CDCl3, 75.5 MHz) : δ = 220.81, 169.96, 164.44, 134.16, 134.27, 123.75, 123.00, 86.13, 80.00, 74.38, 72.03, 64.11, 53.31, 41.74, 39.37, 38.71, 32.87, 32.37, 27.63, 27.47, 22.69, 19.18, 18.37, 15.46, 13.70.

16,17-Didehydro-16-desmethyl-epothilone A (9)

To a solution of 27 mg (0.058) of lactone (**8b**) 4 mL CH_2Cl_2 was added dropwise at - 20°C a solution of dimethyl dioxirane in acetone (2 equiv). Stirring was continued for 2 h at - 20°C . Concentration under vacuum, and separation by HPLC (80:20:3 hexane/t-BuOMe/ MeOH), yielded 17 mg (60 %) of α-epoxide **9** and 9 mg (32 %) of β-epoxide.

α-epoxide

[α] = - 34 (c= 1 in CH_2Cl_2)

IR (KBr): 3453, 2958, 2850, 1744, 1690, 1500, 1467, 1376, 1290, 1261, 1147, 979, 775 cm^{-1}.

^{13}C-NMR ($CDCl_3$, 100.6 MHz) : 220.55, 170.19, 166.12, 135.50, 123.28, 85.00, 80.56, 75.12, 73.59, 62.71, 57.17, 53.75, 52.67, 43.68, 38.69, 35.96, 32.67, 29.72, 26.56, 23.63, 21.12, 20.48, 19.16, 17.06, 14.46

EI-MS (70 eV): m/z (%): 477(27) $[M+H]^+$, 421 (14), 389 (19), 378 (100), 364 (28), 346 (27), 328 (15).

β-epoxide

^{13}C-NMR ($CDCl_3$, 75.5 MHz) : δ = 221.38, 170.03, 166.05,135.70 , 123.28, 85.13, 80.48, 73.24, 73.11, 62.24, 57.14, 55.31, 52.28, 42.89, 38.98, 37.53, 32.40, 31.82, 27.60, 27.01, 23.45, 20.62, 20.36, 16.38, 13.49.

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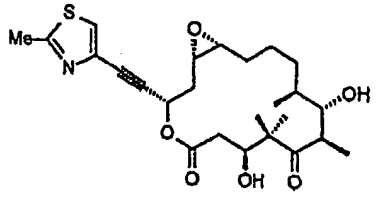
New International Patent Application
Gesellschaft fuer Biotechnlogische Forschung mbH (GBF)

Claims

1. Process for a degradation of an epothilone C or an epothilone D, wherein an epothilone C or an epothilone D is subjected to an olefin metathesis in the presence of ethylene and subsequently an optional ester hydrolysis (scheme I).

2. Process according to claim 1, wherein the epothilone C or D is a fermentation product.

3. Process for the production of an epothilone of formula 9



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wherein

(i) an epothilone of formula 2a (schemes I and II) is converted into compound of formula 3a (scheme II),

(ii) the compound of formula 3a is reacted with a compound of formula 6 (which has been formed by reacting a compound of formula 4 with a compound of formula 5; scheme II) to give a compound of formula 7 (scheme II),

(iii) the compound of formula 7 is reacted in the presence of a Grubbs catalyst to give a compound of formula 8a (scheme II),

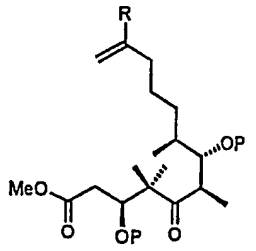
(iv) the compound of formula 8a is converted into a compound of formula 8b (scheme II), and

(v) compound of formula 8b is converted to a compound of formula 9 (scheme II).

4. Process according to claim 3, wherein at stop (i) first free hydroxy groups are protected and second an ester hydrolysis is carried out.

5. Process according to claim 3, wherein at step (iv) deprotection is carried out in an acidic medium preferably by means of trifluoro acetic acid.

6. Process for the production of a compound of formula 3b



R = H, Methyl

P = H, protecting group e.g. trialkylsilyl, p-methoxybenzyl

3b

wherein

(i) the lactone group of an epothilone C or an epothilone D is cleaved,

(ii) the cleavage product of formula 10 (scheme III)

- is optionally subjected to an esterificartion with diazomethane and
- the 3,7-hydroxy groups are optionally protected to give a compound of formula 11 (scheme III) and

(iii) the compound of formula 11

- is subjected to an olefin metathesis and
- the 3,7-hydroxy groups are optionally protected, to give a compound of formula 3b (scheme III).

7. Process according to claim 6, wherein in step (i) the cleavage is carried out
- with pig liver esterase or
- after protection of the 3,7-hydroxy groups, with an aqueous base.

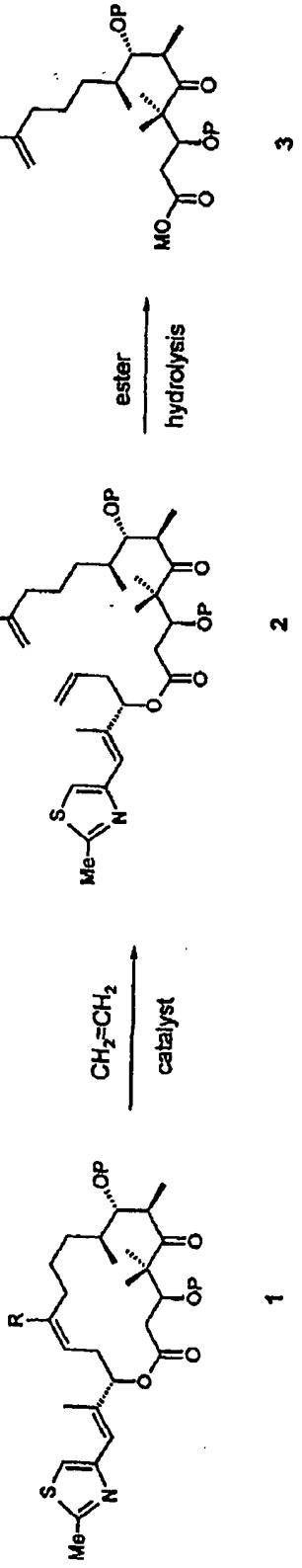
8. Process according to claim 6, wherein in step (iii) ethylene is used as olefin and/or a ruthenium or molybdenum catalyst is used as metathesis catalyst.

9. Process according to claim 3 or claim 6, wherein the 3,7-hydroxy groups are protected by trialkylsilyl or p-methoxy-benzyl.

10. Process according to claim 6, wherein the compound of formula 3b is further processed in accordance to steps (ii) to (v) of claim 3.

11. Compounds of formula 2, 2a, 3, 3a, 3b, 4, 5, 6, 7, 8, 8a, 8b, 9, 10 and 11, obtainable according to a process according to one or more of the preceding claims.

Scheme I



R = H, Methyl

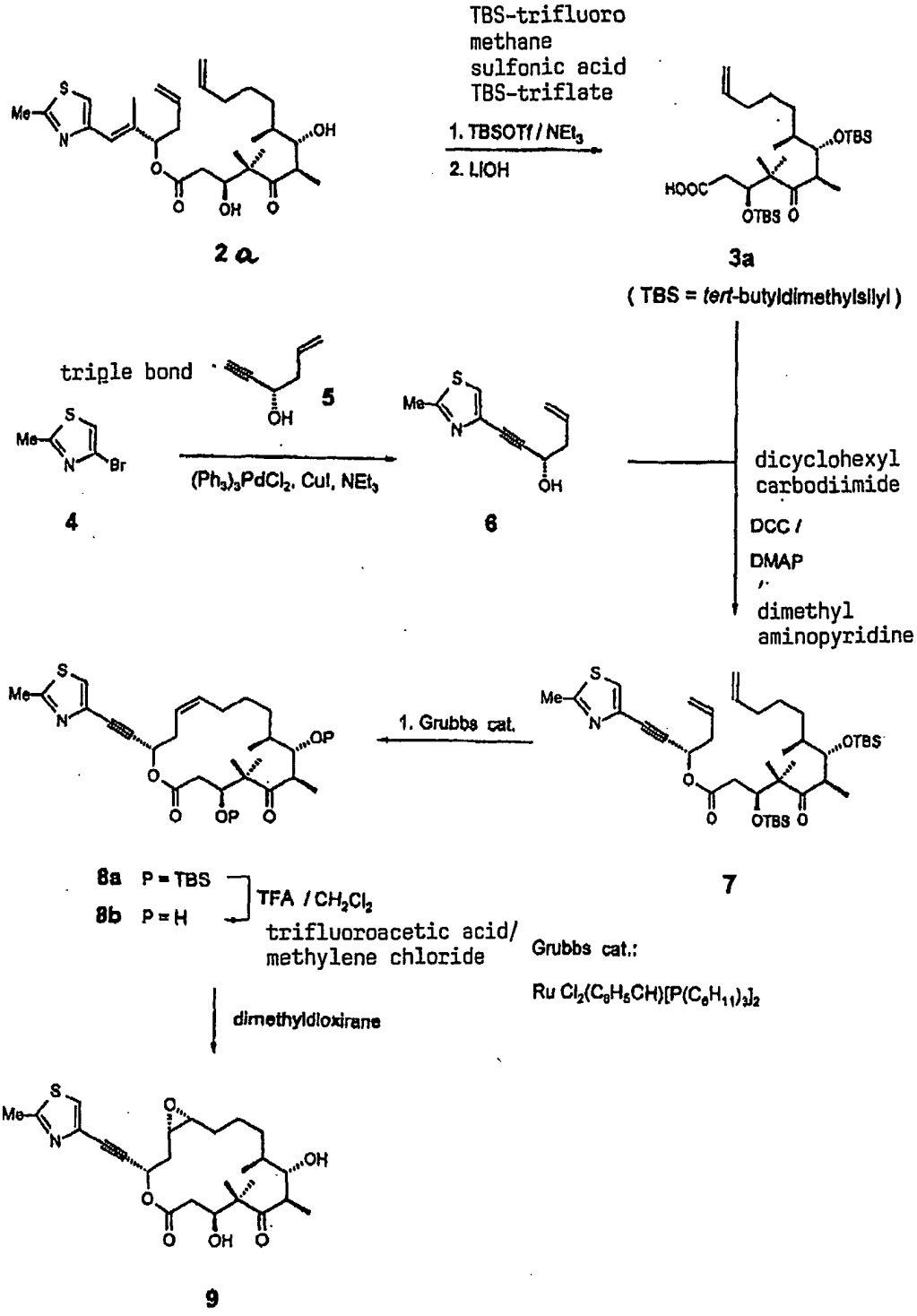
P = H, protecting group e.g. trialkylsilyl

M = alkali metal, H

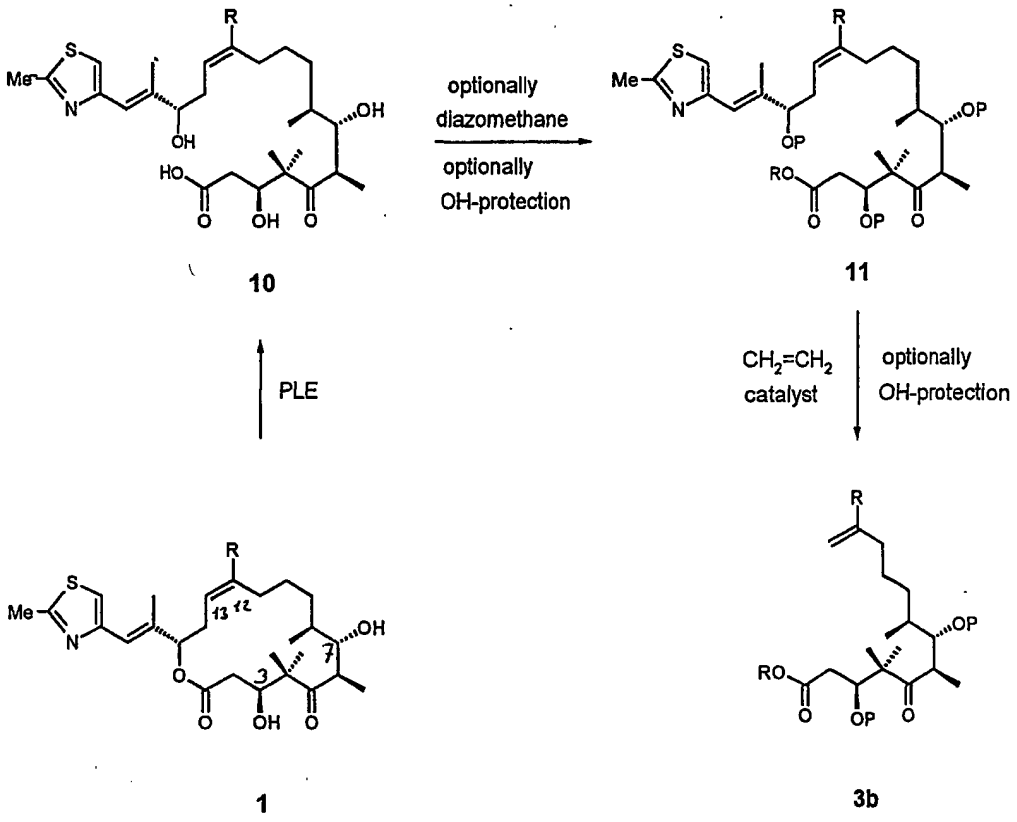
catalyst = e.g. Ru, Mo metathesis catalysts

ester hydrolysis by base or hydrolytic enzymes, e.g. pig liver sterase

Scheme II


TBS-trifluoro methane sulfonic acid TBS-triflate
1. TBSOTf / NEt3
2. LiOH
2a
3a
(TBS = tert-butyldimethylsilyl)
triple bond
5
4
(Ph3)3PdCl2, CuI, NEt3
6
dicyclohexyl carbodiimide
DCC /
DMAP
dimethyl aminopyridine
1. Grubbs cat.
7
8a P = TBS
8b P = H
TFA / CH2Cl2
trifluoroacetic acid/ methylene chloride
Grubbs cat.:
Ru Cl2(C6H5CH)[P(C6H11)3]2
dimethyldioxirane
9

Scheme III



R = H, Methyl

P = H, protecting group e.g. trialkylsilyl, p-methoxybenzyl

catalyst = e.g. Ru, Mo metathesis catalysts

ester hydrolysis by base or hydrolytic enzymes, e.g. pig liver sterase

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01104448.4 27 February 2001 (27.02.2001) EP

(71) Applicant *(for all designated States except US)*: **GESELLSCHAFT FÜR BIOTECHNOLOGISCHE FORSCHUNG MBH (GBF)** [DE/DE]; Mascheroder Weg 1, 38124 Braunschweig (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **HOEFLE, Gerhard** [DE/DE]; Mascheroder Weg 1, 38124 Braunschweig (DE). **KARAMA, Usama** [EG/DE]; Alte Stöckener Strasse 100, 30419 Hannover (DE).

(74) Agents: **BOETERS, Hans, D.** et al.; Boeters & Bauer, Bereiteranger 15, 81541 München (DE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

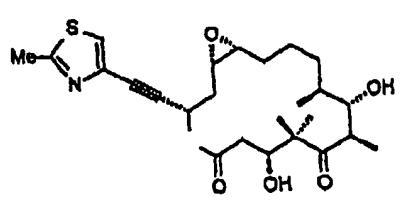
Published:
— *with international search report*

(88) Date of publication of the international search report:
19 December 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/072858 A3

(54) Title: DEGRADATION OF EPOTHILONES AND ETHYNYL SUBSTITUTED EPOTHILONES



(9)

(57) Abstract: The invention concerns a process for a degradation of an epothilone C or a epothilone D, wherein an epothilone C or epothilone D is subjected to an olefin metathesis in the presence of ethylene and subsequently an optional ester hydrolysis. The invention further concerns (2-methyl-1,3-thiazol-4-yl)-ethynyl substitued epothilones (9). Formula (9).

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/02105

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12P17/14 C07D277/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12P C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 25929 A (CIBA GEIGY AG ;SARABIA FRANCISCO (ES); VALLBERG HANS (SE); NICOLAO) 18 June 1998 (1998-06-18)	1,2
X	*compounds 4,45,46,47* page 57 -page 58; figures 2,7,16	11
A	figure 1	3-5,9

Y	WO 98 08849 A (NOVARTIS AKTIENGESELLSCHAFT ;BAUER ARMIN (DE); CORDES MARTIN (DE);) 5 March 1998 (1998-03-05)	1,2
X	*schemes 2 and 4* page 30 -page 32 page 9	11

	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 July 2002	2 0. 09. 02

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Härtinger, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

	ɔnal Application No PCT/EP 02/02105

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	NICOLAOU K C ET AL: "Chemical Biology of Epothilones" ANGEWANDTE CHEMIE. INTERNATIONAL EDITION, VERLAG CHEMIE. WEINHEIM, DE, vol. 37, no. 15, August 1998 (1998-08), pages 2014-2045, XP002131418 ISSN: 0570-0833	1,2
X	*scheme 8* examples 3,38-42	11
A	page 2040, left-hand column, paragraph 2	3-5,9
Y	EP 0 057 736 A (PHILLIPS PETROLEUM CO) 18 August 1982 (1982-08-18) page 13, line 24 - line 38	1,2
Y	MARCH J: "ADVANCED ORGANIC CHEMISTRY" , ADVANCED ORGANIC CHEMISTRY. REACTIONS, MECHANISMS, AND STRUCTURE, NEW YORK, JOHN WILEY & SONS, US XP002200250 ISBN: 0-471-60180-2 *chapter 8-39 Metathesis of Olefins* page 1146 -page 1149	1,2
A	ZHEN YANG ET AL: "ANGEWANDTE CHEMIE, VCH VERLAGSGESELLSCHAFT, WEINHEIM, DE" ANGEWANDTE CHEMIE, VCH VERLAGSGESELLSCHAFT, WEINHEIM, DE, vol. 109, no. 1/2, 1997, pages 170-172, XP002095722 ISSN: 0044-8249 *scheme 2*	1-5,9,11
A	WO 98 38192 A (BIOTECHNOLOG FORSCHUNG GMBH ;HOEFLE GERHARD (DE); SEFKOW MICHAEL () 3 September 1998 (1998-09-03) page 9 -page 10; examples	3-5,9,11
X	WO 00 58254 A (UNIV KANSAS) 5 October 2000 (2000-10-05) page 16; example 17	11
X	SMITH A B ET AL: "Total Synthesis of (-)-Macrolactin A" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 118, 1996, pages 13095-13096, XP002207324 ISSN: 0002-7863 *scheme 2* example 3	11

national application No.
PCT/EP 02/02105

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT, no additional fees are to be refunded.

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

1-5,9,11

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☒ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1(part),2(part),11(part)

   olefin methathesis of product 1 to give intermediate 2; intermediates 2 (2a)

2. Claims: 1(part),2(part),3(part),4(part),11(part)

   ester hydrolysis of intermediate 2 (2a) to give intermediate 3 (3a,3b) and product 3 (3a, 3b)

3. Claims: 3(part),5(part),9(part),11(part)

   process for the production of 9 starting from intermediates 6 and 3 (3a, 3b); intermediates 4, 5, 6, 7, 8 (8a, 8b), 9

4. Claims: 6(part)-10(part),11(part)

   process for the production of intermediates 10 or 11 starting from 1; products 10, 11

5. Claims: 6(part)-10(part),11(part)

   process for the preparation of intermediate 3 (3a, 3b) starting from 11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/02105

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9825929	A	18-06-1998	AU	746597 B2	02-05-2002
			AU	5757798 A	03-07-1998
			BR	9714140 A	29-02-2000
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			NZ	337195 A	25-05-2001
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			ZA	9801575 A	08-09-1998
WO 0058254	A	05-10-2000	US	6211412 B1	03-04-2001
			AU	3771100 A	16-10-2000
			WO	0058254 A1	05-10-2000

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 September 2002 (19.09.2002)

PCT

(10) International Publication Number
WO 02/072858 A3

(51) International Patent Classification[7]: C12P 17/14, C07D 277/30

(21) International Application Number: PCT/EP02/02105

(22) International Filing Date: 27 February 2002 (27.02.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
01104448.4 27 February 2001 (27.02.2001) EP

(71) Applicant *(for all designated States except US)*: **GESELLSCHAFT FÜR BIOTECHNOLOGISCHE FORSCHUNG MBH (GBF)** [DE/DE]; Mascheroder Weg 1, 38124 Braunschweig (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **HOEFLE, Gerhard** [DE/DE]; Mascheroder Weg 1, 38124 Braunschweig (DE). **KARAMA, Usama** [EG/DE]; Alte Stöckener Strasse 100, 30419 Hannover (DE).

(74) Agents: **BOETERS, Hans, D.** et al.; Boeters & Bauer, Bereiteranger 15, 81541 München (DE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

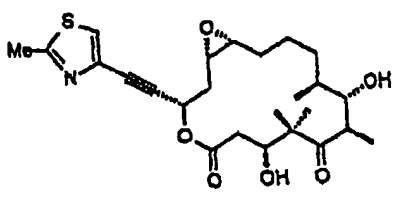
Published:
— *with international search report*

(88) Date of publication of the international search report:
19 December 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/072858 A3

(54) Title: DEGRADATION OF EPOTHILONES AND ETHYNYL SUBSTITUTED EPOTHILONES



(9)

(57) Abstract: The invention concerns a process for a degradation of an epothilone C or a epothilone D, wherein an epothilone C or epothilone D is subjected to an olefin metathesis in the presence of ethylene and subsequently an optional ester hydrolysis. The invention further concerns (2-methyl-1,3-thiazol-4-yl)-ethynyl substitued epothilones (9). Formula (9).

INTERNATIONAL SEARCH REPORT

	nal Application No
	PCT/EP 02/02105

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12P17/14 C07D277/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12P C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 25929 A (CIBA GEIGY AG ;SARABIA FRANCISCO (ES); VALLBERG HANS (SE); NICOLAO) 18 June 1998 (1998-06-18)	1,2
X	*compounds 4,45,46,47* page 57 -page 58; figures 2,7,16	11
A	figure 1	3-5,9

Y	WO 98 08849 A (NOVARTIS AKTIENGESELLSCHAFT ;BAUER ARMIN (DE); CORDES MARTIN (DE);) 5 March 1998 (1998-03-05)	1,2
X	*schemes 2 and 4* page 30 -page 32 page 9	11

	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 July 2002	31. 07. 02

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Härtinger, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/02105

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NICOLAOU K C ET AL: "Chemical Biology of Epothilones" ANGEWANDTE CHEMIE. INTERNATIONAL EDITION, VERLAG CHEMIE. WEINHEIM, DE, vol. 37, no. 15, August 1998 (1998-08), pages 2014-2045, XP002131418 ISSN: 0570-0833	1,2
X	*scheme 8* examples 3,38-42	11
A	page 2040, left-hand column, paragraph 2	3-5,9
Y	EP 0 057 736 A (PHILLIPS PETROLEUM CO) 18 August 1982 (1982-08-18) page 13, line 24 - line 38	1,2
Y	MARCH J: "ADVANCED ORGANIC CHEMISTRY" , ADVANCED ORGANIC CHEMISTRY. REACTIONS, MECHANISMS, AND STRUCTURE, NEW YORK, JOHN WILEY & SONS, US XP002200250 ISBN: 0-471-60180-2 *chapter 8-39 Metathesis of Olefins* page 1146 -page 1149	1,2
A	ZHEN YANG ET AL: "ANGEWANDTE CHEMIE, VCH VERLAGSGESELLSCHAFT, WEINHEIM, DE" ANGEWANDTE CHEMIE, VCH VERLAGSGESELLSCHAFT, WEINHEIM, DE, vol. 109, no. 1/2, 1997, pages 170-172, XP002095722 ISSN: 0044-8249 *scheme 2*	1-5,9,11
A	WO 98 38192 A (BIOTECHNOLOG FORSCHUNG GMBH ;HOEFLE GERHARD (DE); SEFKOW MICHAEL () 3 September 1998 (1998-09-03) page 9 -page 10; examples	3-5,9,11
X	WO 00 58254 A (UNIV KANSAS) 5 October 2000 (2000-10-05) page 16; example 17	11
X	SMITH A B ET AL: "Total Synthesis of (-)-Macrolactin A" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 118, 1996, pages 13095-13096, XP002207324 ISSN: 0002-7863 *scheme 2* example 3	11

national application No.
PCT/EP 02/02105

INTERNATIONAL SEARCH REPORT

Box I Observati ns where certain claims wer found unsearchable (Continuati n f Item 1 f first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT, no additional fees are to be refunded.

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

1-5,9,11

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☒ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1(part),2(part),11(part)

olefin methathesis of product 1 to give intermediate 2; intermediates 2 (2a)

2. Claims: 1(part),2(part),3(part),4(part),11(part)

ester hydrolysis of intermediate 2 (2a) to give intermediate 3 (3a,3b) and product 3 (3a, 3b)

3. Claims: 3(part),5(part),9(part),11(part)

process for the production of 9 starting from intermediates 6 and 3 (3a, 3b); intermediates 4, 5, 6, 7, 8 (8a, 8b), 9

4. Claims: 6(part)-10(part),11(part)

process for the production of intermediates 10 or 11 starting from 1; products 10, 11

5. Claims: 6(part)-10(part),11(part)

process for the preparation of intermediate 3 (3a, 3b) starting from 11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/02105

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9825929	A	18-06-1998	AU	746597 B2	02-05-2002
			AU	5757798 A	03-07-1998
			BR	9714140 A	29-02-2000
			CN	1246862 A	08-03-2000
			WO	9825929 A1	18-06-1998
			EP	0944634 A1	29-09-1999
			JP	2001504856 T	10-04-2001
			US	6380394 B1	30-04-2002
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			DE	19645361 A1	30-04-1998
			DE	19645362 A1	30-04-1998
			AU	716610 B2	02-03-2000
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			EP	0923583 A1	23-06-1999
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			NZ	334821 A	22-12-2000
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			US	5969145 A	19-10-1999
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			AU	6724998 A	18-09-1998
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